Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression.

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Public Summary:
Our results indicate that cycles of an extreme dietary intervention represent a powerful mean to modulate key regulators of cellular protection and tissue regeneration but also provide a potential therapy to reverse or alleviate the immunosuppression or immunosenescence caused by chemotherapy treatment and aging, respectively, and possibly by a variety of diseases affecting the hematopoietic system and other systems and organs. The clinical data shown here provide preliminary results supporting the possibility that these effects can also be translated into effective clinical applications.

Scientific Abstract:
Immune system defects are at the center of aging and a range of diseases. Here, we show that prolonged fasting reduces circulating IGF-1 levels and PKA activity in various cell populations, leading to signal transduction changes in long-term hematopoietic stem cells (LT-HSCs) and niche cells that promote stress resistance, self-renewal, and lineage-balanced regeneration. Multiple cycles of fasting abated the immunosuppression and mortality caused by chemotherapy and reversed age-dependent myeloid-bias in mice, in agreement with preliminary data on the protection of lymphocytes from chemotoxicity in fasting patients. The proregenerative effects of fasting on stem cells were recapitulated by deficiencies in either IGF-1 or PKA and blunted by exogenous IGF-1. These findings link the reduced levels of IGF-1 caused by fasting to PKA signaling and establish their crucial role in regulating hematopoietic stem cell protection, self-renewal, and regeneration.